IN THE UNITED STATES DISTRICT COURT
FOR THE MIDDLE DISTRICT OF NORTH CAROLINA

BIOMÉRIEUX, S.A., BIOMÉRIEUX, INC.,	)	
	)	
	)	
Plaintiffs,	)	
	)	
v.	)	**Case No. 1:17-CV-102**
	)	
HOLOGIC, INC., GRIFOLS, S.A., GRIFOLS DIAGNOSTIC SOLUTIONS INC.	)	**JURY TRIAL REQUESTED**
	)	
	)	
	)	
Defendants.	)	

COMPLAINT

Plaintiffs bioMérieux, S.A. and bioMérieux, Inc. (collectively "bioMérieux"), by their attorneys, for their Complaint, allege as follows:

NATURE OF THE ACTION

1. This is an action for patent infringement under the laws of the United States, Title 35, United States Code, by bioMérieux against Hologic, Inc. ("Hologic"), Grifols, S.A. ("Grifols, S.A."), and Grifols Diagnostic Solutions Inc. ("Grifols USA," and collectively with Hologic and Grifols, S.A., "the Defendants").

2. This action arises from the Defendants' manufacture, use, offer for sale, and sale in the United States of products used in the detection, amplification, and quantification of Human Immunodeficiency Virus Type 1 ("HIV-1") in human blood. That activity directly infringes, induces others to infringe, and contributes to the infringement of claims of two bioMérieux U.S. patents.

THE PARTIES

3. bioMérieux, S.A. is a corporation organized and existing under the laws of France, having its principal place of business at Chemin de L'Orme, Marcy-L'Etoile, France.

4. bioMérieux, Inc. is a corporation organized and existing under the laws of the State of Missouri, with its U.S. headquarters located at 100 Rodolphe Street, Durham, North Carolina.

5. Hologic is a corporation organized and existing under the laws of the State of Delaware, having its principal place of business at 250 Campus Drive, Marlborough, Massachusetts. Hologic is the successor-in-interest to Gen-Probe Incorporated ("Gen-Probe").

6. On information and belief, Defendant Grifols, S.A. is a corporation organized and existing under the laws of Spain, having its principal place of business at Avinguda de la Generalitat, 152, Parque empresarial Can Sant Joan, Sant Cugat del Valles, Barcelona, Spain.

7. Defendant Grifols USA is a corporation organized and existing under the laws of the State of Delaware, having its principal place of business at 4560 Horton Street, Emeryville, California. Grifols USA is a wholly-owned subsidiary of Grifols, S.A., and is controlled by and/or acts as an agent of Grifols, S.A. in the United States.

JURISDICTION AND VENUE

8. This Court has subject matter jurisdiction pursuant to 28 U.S.C. §§ 1331, 1338(a).

9. Based on the facts and causes alleged herein, and for additional reasons to be further developed through discovery if necessary, this Court has personal jurisdiction over the Defendants.

10. This Court has personal jurisdiction over the Defendants because directly or through intermediaries they have committed acts within this District and this State giving rise to this action and/or have established minimum contacts with North Carolina such that the exercise of jurisdiction would not offend traditional notions of fair play and substantial justice. The Defendants offer for sale and sell infringing HIV-1 assay products in the State of North Carolina, including in this District to hospitals, blood banks, and other medical facilities. Moreover, the Defendants have placed, and are continuing to place, infringing HIV-1 assay products into the stream of commerce, via an established distribution channel, with the knowledge and/or understanding that such products are sold in the State of North Carolina, including in this District, providing the Defendants with substantial revenues.

11. This Court additionally has personal jurisdiction over the Defendants because the Defendants have knowingly induced and/or contributed to, and continue to knowingly induce and/or contribute to, infringement within this District by advertising, marketing, offering for sale, and/or selling infringing HIV-1 assay products within this

District, to consumers, customers, distributors, resellers, partners, and/or end users, and providing instructions, advertising, and/or marketing materials that facilitate, direct, or encourage the use of infringing products with knowledge thereof.

12. Venue is proper in this District pursuant to 28 U.S.C. §§ 1391 and 1400(b).

BACKGROUND

A. bioMérieux's Innovations and Asserted Patents

13. bioMérieux is a world leader in the field of *in vitro* diagnostic testing. The company creates diagnostic solutions that improve patient health and ensure consumer safety by identifying the sources of disease and contamination. Among other things, bioMérieux has developed innovative tests for screening for infectious diseases in the blood and blood products received by transfusion recipients, surgical patients, and clinical trial participants.

14. In the 1990s bioMérieux, through a predecessor-in-interest, undertook extensive efforts to discover a new and better way to screen blood for the presence of HIV-1, the virus that causes AIDS. Blood screening was and remains critical not just for patients but for blood banks, where poorly screened blood could cause infection on a massive scale. Early versions of HIV-1 tests screened for the presence of antibodies targeted to the virus. Such testing is highly reliable in detecting the virus in patients or donors who were infected six months or more before their blood sample was taken. It can take that much time for humans to produce measureable levels of anti-HIV

antibodies in response to an infection (a process known as seroconversion). For samples drawn after infection but before seroconversion, this type of testing can produce false negatives. False negatives are always an undesirable outcome in diagnostic testing but are especially serious in HIV-1 testing given the communicable nature of the disease and the high mortality associated with disease progression.

15. Shortening the window between infection and detection promised significant benefits to public health by reducing the risk to the blood supply of infected donors and the risk that patients, unaware they were carrying the virus, would infect others. Scientists eventually developed tests based on "nucleic acid amplification" that were capable of detecting HIV-1 in the blood before the body started producing antibodies in response to the infection.

16. Nucleic acids, often called the building blocks of life, are essential to creating the proteins and other chemicals that living organisms need to survive. The two principal nucleic acids are DNA (deoxyribonucleic acid) and RNA (ribonucleic acid). These molecules are comprised of sequences of smaller molecules called nucleotides. In DNA, there are four different nucleotides: adenine (A), thymine (T), cytosine (C), and guanine (G). RNA uses the same nucleotides, except that uracil (U) is substituted for thymine.

17. DNA also differs from RNA in that RNA is a single strand of nucleotides while DNA is composed of two strands that bind to form the familiar double-helix. The two strands of DNA are "complementary," that is, each adenine on one strand

is matched with a thymine on the opposite strand, and each guanine is matched with a cytosine.

18. DNA and RNA work together to help the body make proteins. Inside the cell nucleus, through a natural process called "transcription," DNA makes RNA. The RNA then leaves the nucleus and, once in the cell's cytoplasm, is "translated" into a particular protein by molecular complexes called ribosomes.

19. Nucleic acid amplification technologies work by causing either the DNA or RNA of interest, for example DNA or RNA associated with a virus or bacteria, to be replicated exponentially ("amplified") within the sample and therefore become present in detectable levels. HIV tests using the technique permit detection of a virus within days of infection.

20. One industry leader, Hoffman-La Roche, developed and sold a test utilizing a particular type of nucleic acid amplification called "polymerase chain reaction," or PCR. PCR works by amplifying DNA directly using suitable reagents and a pair of man-made nucleotide sequences, called "primers," that are complementary to portions of the DNA of interest. In PCR, the temperature of the reaction is first increased to cause the two strands of DNA to come apart, or "denature." Next, the temperature of the reaction is reduced, causing the primers to bind to a complementary sequence of the single-stranded DNA. Enzymes and reagents added to the reaction create new double-stranded DNA molecules essentially identical to portions of the DNA molecules that

were denatured. These steps are repeated to amplify the DNA to a detectable level. Scientists who invented PCR received the 1993 Nobel Prize in Chemistry.

21. bioMérieux's test utilized a different, later-developed transcription-based amplification technology. Like PCR, transcription-based amplification works by contacting primers with a sample (for example, of blood) under suitable reaction conditions and using suitable reagents. But transcription-based amplification differs from PCR in important respects. First, unlike PCR, it amplifies RNA rather than DNA. Second, the process does not require changes in temperature for the amplification to work. Third, unlike PCR, the transcription-based amplification method, to work properly and produce a detectable level of replicated RNA, requires something called a "promoter," a series of nucleotides that do not match the sequence of the RNA of interest.

22. As the AIDS epidemic progressed, testing for the HIV-1 virus met new challenges. In particular, the virus had an unusual capacity to mutate into subtypes, each having its own distinct genetic signature. When the first nucleic acid amplification tests were designed, scientists were testing samples from patients infected primarily with what is now characterized as "subtype B," then the dominant strain of HIV-1 in Europe and the United States. But as the epidemic spread infections from other parts of the world, scientists identified other strains with different genetic sequences. Eventually they divided variants of the virus into at least two groups: the major group (Group M) and an outlier group (Group O). Group M is further divided into at least eight subtypes (A-H).

23. In the mid-1990s, scientists at bioMérieux's predecessor and the University of Amsterdam, working in collaboration, realized that existing nucleic acid amplification tests were failing to detect some strains of HIV-1, particularly non-B subtypes. This was a major public health concern that affected patient care and the global blood supply.

24. In response to this problem, the collaborating scientists began researching whether a more sensitive and therefore more effective HIV-1 test, one capable of detecting many different HIV-1 subtypes, could be made using transcription-based amplification with primers selected from different parts of the HIV-1 genome.

25. As part of this research project, the scientists analyzed blood samples collected from around the world and scoured the entire HIV-1 genome for insights. Many of the sequences of these HIV-1 samples were not previously published or otherwise publicly available.

26. Although the scientists eventually identified regions of the HIV-1 genome they considered good candidates for detecting the missing subtypes, more work remained. The process for designing transcription-based amplification primers was unpredictable at that time. The three-dimensional structure of HIV-1 RNA, for example, was believed to substantially affect the ability to use primers in transcription-based amplification techniques, and was not fully understood in the mid-1990s. And there were multiple other aspects of designing primers for use with transcription-based amplification that made the primers more or less effective, including how far apart the primers are

positioned on the HIV-1 genome, the extent to which the primers bind to each other (a problem called "primer dimerization"), their "G/C content," that is, the percentage of guanine and cytosine nucleotides in the primers, and the inclusion of a promoter sequence. The scientists had to take all of these considerations into account in designing primer sequences that were not just functional for use with transcription-based amplification techniques but actually better than the amplification techniques available at the time.

27. Eventually, the collaborating scientists achieved a breakthrough: They identified nucleotide sequences derived from a particular part of the HIV-1 genome that, when used in primer sets with a transcription-based amplification technique, were capable of detecting nearly all known HIV-1 subtypes. The resulting methods were much more sensitive than methods disclosed in the prior art, and delivered results much faster.

28. bioMérieux protected its significant investment in these inventions by, among other things, applying for, and obtaining, several U.S., European, and other foreign patents including: U.S. Patent No. 8,697,352, and U.S. Patent No. 9,074,262 (collectively, the "Asserted Patents").

The Patents

29. United States Patent No. 8,697,352 (the "'352 patent"), titled "Nucleic Acid Sequences that Can Be Used as Primers and Probes in the Amplification and Detection of All Subtypes of HIV-1," was duly issued on April 15, 2014 and remains unexpired. The '352 patent is attached hereto as Exhibit A. The '352 patent claims

priority to European Patent Application 97202455, filed August 8, 1997. bioMérieux, S.A. and bioMérieux, Inc. are co-assignees of the '352 patent.

30. United States Patent No. 9,074,262 (the "'262 patent"), titled "Nucleic Acid Sequences that Can Be Used as Primers and Probes in the Amplification and Detection of All Subtypes of HIV-1," was duly issued on July 7, 2015 and remains unexpired. The '262 patent is attached hereto as Exhibit B. The '262 patent also claims priority to European Patent Application 97202455, filed August 8, 1997. bioMérieux, S.A. and bioMérieux, Inc. are co-assignees of the '262 patent.

B. The Defendants' Infringing Products and Activities

31. The Defendants provide services, products, kits, and devices that are used in the detection and diagnosis of HIV-1 and other diseases.

32. Hologic's predecessor-in-interest, Gen-Probe, began experimenting with methods of detecting HIV-1 using nucleic acid testing by at least the late 1980s. For more than a decade, Gen-Probe's patents and publications focused on primer pairs for use in transcription-based amplification other than those claimed in the Asserted Patents.

33. On information and belief, it was not until after publication of the first application in the family of the Asserted Patents that Gen-Probe began making, using, offering for sale, and selling in the United States the inventions claimed in the Asserted Patents.

34. Defendants currently make, use, offer for sale, and/or sell infringing products in the United States.

35. In particular, Defendants have been parties to a distribution agreement under which Hologic manufactures in the United States products used for amplifying and detecting HIV-1. Those products are sold to Grifols, S.A. and Grifols USA and then resold in the United States and the rest of the world, marketed under the names Procleix HIV-1/HCV Assay, Procleix Ultrio Assay, and Procleix Ultrio Plus Assay (the "Procleix Tests"). Under their contractual arrangement, Hologic ships the Accused Products to customers identified and contracted by Grifols, S.A. and Grifols USA. The Defendants split the net proceeds of those sales.

36. Hologic also independently makes, uses, offers for sale, and sells in the United States its own products used for amplifying and detecting HIV-1 under the names Aptima HIV-1 RNA Qualitative Assay and Aptima HIV-1 Quant DX Assay ("Aptima Tests"). Together with the Procleix Tests, these are the "Accused Tests."

37. In December 2016, Hologic announced that Grifols, S.A. was purchasing its interest in its blood screening business. According to this announcement, Hologic is retaining its interest in the Aptima Tests. Hologic announced the closing of the sale on January 31, 2017.

38. The manufacture, use, offer for sale, and sale of the Accused Tests in the United States, with accompanying instructions, infringe and/or induce or contribute to infringement of the Asserted Patents because the tests amplify and detect HIV-1 through the use of oligonucleotide primers, promoters, methods, and kits, that are covered by the claims of the Asserted Patents.

39. The Accused Tests are and have been sold, offered for sale, and/or marketed by the Defendants in this District through advertising in internet, print, and/or television media, and/or by sales staff employed by the Defendants.

40. The Defendants have infringed and continue to infringe (literally and/or under the doctrine of equivalents), directly, indirectly, and/or through agents or intermediaries, one or more claims of the Asserted Patents, including at least claim 1 of each of the Asserted Patents, by making, using, offering for sale, and/or selling in the United States the Accused Tests.

41. The Defendants' customers (including distributors and retailers) have infringed and continue to infringe (literally and/or under the doctrine of equivalents), directly, indirectly, and/or through agents or intermediaries, one or more claims of the Asserted Patents, including at least claim 1 of each of the Asserted Patents, by using, offering for sale, and/or selling in the United States the Accused Tests. Through their sales and marketing activities, including advertising and product labeling, the Defendants solicit, instruct, encourage, and aid and abet their customers to purchase, use, offer for sale, and/or sell the Accused Tests.

42. The Defendants' infringement has been willful. They have engaged in the accused activities with knowledge of the Asserted Patents and without a license or permission to practice the inventions claimed therein.

43. On information and belief, the Defendants' actions have been with specific intent to cause infringement or the Defendants have been willfully blind to the

resulting infringement because the Defendants have had knowledge of the Asserted Patents and knowledge that their acts were infringing, contributing to, or inducing infringement of the Asserted Patents since before the filing of this action. In particular, bioMérieux knows and is informed that Hologic has had knowledge of the Asserted Patents through its efforts over the last several years to revoke foreign counterparts of these patents that issued from the European Patent Office. On information and belief, Grifols, S.A. and Grifols USA have had knowledge of the Asserted Patents through their relationship with their predecessor companies and Hologic.

44. Despite their knowledge of the Asserted Patents, the Defendants have made, used, offered for sale, and/or sold in the United States products covered by one or more claims of the Asserted Patents, including the Accused Tests, which constitutes direct and indirect infringement.

45. The Defendants' infringement of the Asserted Patents has been and is willful, wanton, malicious, in bad faith, and deliberate. Following the failure of their own efforts to develop commercially viable kits to amplify and detect HIV-1, the Defendants gained knowledge of bioMérieux's invention from bioMérieux's publications or published patent applications and then undertook and have continued to make, use, offer for sale, and/or sell in the United States the invention claimed in the Asserted Patents despite their knowledge of the Asserted Patents.

46. The Defendants' infringement has caused, is causing, and will continue to cause bioMérieux to suffer damage and bioMérieux is entitled to recover

damages in an amount proven at trial, but no less than a reasonable royalty as provided by 35 U.S.C. § 284, before any enhancement for the willfulness of the Defendants' infringement.

COUNT I
(Infringement of the '352 Patent)

47. bioMérieux incorporates each of the preceding paragraphs as if fully set forth herein.

48. The Defendants have been and are now directly infringing the '352 patent in violation of 35 U.S.C. § 271(a) by making, using, offering for sale, and/or selling in the United States products that infringe the claims of the '352 patent, including but not limited to the Accused Products.

49. By way of example, with respect to claim 1 of the '352 patent, the Accused Products utilize a primer pair "consist[ing] essentially of a first oligonucleotide that is fully complementary to a sequence of the LTR region at a first primer binding site and binds thereto under conditions whereby nucleic acid amplification can occur, said oligonucleotide being 15-26 nucleotides in length and comprising at least 15 sequential nucleotides of the nucleotide sequence of" G GGC GCC ACT GCT AGA GA, said first oligonucleotide "being operably linked to a T3, T7, or SP9 promoter," and a second primer "consist[ing] essentially of a second oligonucleotide that is fully complementary to a sequence which is the reverse complement of a sequence of the LTR region at a second primer binding site and binds thereto under conditions whereby nucleic acid amplification can occur, said oligonucleotide being 10-26 nucleotides in length and

comprising at least 10 sequential nucleotides of the nucleotide sequence of" CTC AAT AAA GCT TGC CTT GA. By making, using, offering for sale, and/or selling in the United States products, including the Accused Products, that include the invention as recited in claim 1 of the '352 patent, the Defendants infringe at least claim 1 of the '352 patent.

50. The Defendants' direct infringement of the '352 patent is willful.

51. The Defendants have been and are now indirectly infringing the '352 patent in violation of 35 U.S.C. § 271(b) by actively inducing the direct infringement of the '352 patent by their distributors, retailers, and customers, including at least by making, using, offering for sale, and/or selling in the United States the Accused Products.

52. The Defendants also have been and are now indirectly infringing the '352 patent in violation of 35 U.S.C. § 271(c) by contributing to the direct infringement of the '352 patent by their distributors, retailers, and customers. When used to amplify and detect HIV-1 as directed by the Defendants, the use of the Accused Products infringes the '352 patent. On information and belief, the infringing HIV-1 test is used any time the Accused Products are used and thus the Accused Products have no substantial non-infringing uses and are not a staple article of commerce.

53. The Defendants' inducement of and contribution to infringement of the '352 patent is willful.

54. As a consequence of the Defendants' infringement of the '352 patent, bioMérieux has suffered, is suffering, and will continue to suffer damages in an amount not yet determined, but no less than a reasonable royalty.

55. The Defendants' willful, wanton, and deliberate infringement of the '352 patent justifies an award to bioMérieux of increased damages under 35 U.S.C. § 284, and attorneys' fees and costs incurred under 35 U.S.C. § 285.

COUNT II
(Infringement of the '262 Patent)

56. bioMérieux incorporates each of the preceding paragraphs as if fully set forth herein.

57. The Defendants have been and are directly infringing the '262 patent by performing the claimed methods.

58. The Defendants also have been and are now indirectly infringing the '262 patent in violation of 35 U.S.C. § 271(b) by actively inducing the direct infringement of the '262 patent by their distributors, retailers, and customers, including at least by making, using, offering for sale, and/or selling in the United States the Accused Products.

59. Furthermore, the Defendants have been and are now indirectly infringing the '262 patent in violation of 35 U.S.C. § 271(c) by contributing to the direct infringement of the '262 patent by their distributors, retailers, and customers. When used to amplify and detect HIV-1 as directed by the Defendants, the Accused Products are a substantial component of a method that infringes the '262 patent. On information and

belief, the infringing HIV-1 test is used any time the Accused Products are used and thus the Accused Products have no substantial non-infringing uses and are not a staple article of commerce.

60. By way of example, with respect to claim 1 of the ’262 patent, the Defendants, per their advertisements, publications, and product labeling, have actively induced and contributed to the use by their distributors, retailers, and customers of a method for amplifying HIV-1 nucleic acid in a sample. *See* Package Insert - Procleix Ultrio Assay, *available at* goo.gl/BGXN67 (“The Procleix Ultrio Assay utilizes the [Transcription-Mediated Amplification] method to amplify regions of HIV-1 RNA, HCV RNA, and/or HBV DNA.”). As suggested by these promotional materials, the method Defendants induce their distributors, retailers, and customers to use involves, *inter alia*, “contacting the sample with a pair of oligonucleotide primers that bind to a first primer binding site and a second primer binding site located within the LTR region of the HIV-1 genome,” and “performing a nucleic acid amplification under conditions wherein said oligonucleotide primers bind only to said first and second primer binding sites, thereby amplifying HIV-1 nucleic acid in the sample,” wherein “said pair of oligonucleotide primers consists of a first primer and a second primer.” Furthermore, the method involves, *inter alia*, a first primer that “consists essentially of a first oligonucleotide that is fully complementary to a sequence of the LTR region at a first primer binding site, said oligonucleotide being 15-26 nucleotides in length and comprising at least 15 sequential nucleotides of the nucleotide sequence of” G GGC GCC ACT GCT AGA GA, said first

oligonucleotide "being operably linked to a promoter," and a second primer that "consists essentially of a second oligonucleotide that is fully complementary to a sequence which is the reverse complement of a sequence of the LTR region at a second primer binding site, said oligonucleotide being 10-26 nucleotides in length and comprising at least 10 sequential nucleotides of the nucleotide sequence of" CTC AAT AAA GCT TGC CTT GA. By actively inducing distributors, retailers, and customers to make, use, offer for sale, and/or sell in the United States products, including the Accused Products, capable of performing each step of the method recited in claim 1 of the '262 patent, the Defendants infringe at least claim 1 of the '262 patent.

61. The Defendants' direct infringement, and inducement of and contribution to infringement of the '262 patent is willful.

62. As a consequence of the Defendants' infringement of the '262 patent, bioMérieux has suffered, is suffering, and will continue to suffer damages in an amount not yet determined, but no less than a reasonable royalty.

63. The Defendants' willful, wanton, and deliberate infringement of the '262 patent justifies an award to bioMérieux of increased damages under 35 U.S.C. § 284, and attorneys' fees and costs incurred under 35 U.S.C. § 285.

WHEREFORE, bioMérieux requests the following relief:

(a) A judgment that the Defendants have infringed the '352 patent;

(b) A judgment that the Defendants have infringed the '262 patent;

(c) Damages in the form of lost profits but in no event less than a reasonable royalty on past and future infringing sales;

(d) A judgment that the infringement has been willful and an enhancement of damages;

(e) A declaration that this is an exceptional case and an award of attorneys' fees pursuant to 35 U.S.C. § 285;

(f) An award of bioMérieux's costs and expenses in this action; and

(g) Such further and other relief as this Court may deem just and proper.

DEMAND FOR JURY TRIAL

bioMérieux requests a trial by jury on all issues properly triable by jury.

SMITH, ANDERSON, BLOUNT, DORSETT, MITCHELL & JERNIGAN, L.L.P.

/s/ Michael W. Mitchell
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